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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

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AND INTERFERENCES

Ex parte STEVE J. LACKIE and THOMAS R. GLASS

Appeal No. 2001-2401
Application 08/277,225

ON BRIEF

Before WILLIAM F. SMITH, SCHEINER and MILLS, Administrative Patent Judges,

MILLS , Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 1-14 and 16-25, which are the claims pending in this application.

Claims 1, 11 and 23 are representative of the claims on appeal and read as

follow:

1. A method of detecting the presence or level of an analyte in a sample, the method comprising the steps of:

(a) providing a sample containing an analyte;

(b) mixing said sample with a second ligand, which second ligand binds to said analyte when incubated therewith, so that analyte/second ligand complexes are formed;

(c) providing a solid phase having bound thereto a first ligand, which first ligand is characterized by an ability to bind to said second ligand in such a way that, were said first ligand and analyte exposed simultaneously to unbound second ligand, said first ligand would compete with said analyte for binding to said second ligand;

(d) contacting the mixture produced in step (a) with said solid phase so that unbound second ligand in said mixture binds to said first ligand on said solid phase, said contacting being performed for a time sufficiently limited that substantially no dissociation of said analyte/second ligand complexes occurs while said mixture is in contact with said solid phase;

(e) binding a detectable tag to said second ligand either prior to or after step (a), step (b), step (c), or step (d) so that a portion of said tag is retained on said solid phase upon formation of said first ligand/second ligand complex; and

(f) detecting said portion of said tag and comparing it to an amount of tag retained on the column in the presence of a known amount of analyte to determine the presence or level of said analyte in said sample.

11. A method of detecting the presence or level of an analyte in a sample, the method comprising steps of:

(a) contacting said sample with:

(i) a solid phase having bound thereto a first ligand that binds said analyte when incubated therewith; and

(ii) a second ligand that binds said analyte when incubated therewith, the result of the two contacting steps being that a first ligand/analyte/second ligand complex is formed on said solid phase[;]

(b) limiting the contact time between said second ligand and said solid phase so that:

(i) non-specific binding between said second ligand and said solid phase is not allowed to reach equilibrium; and

(ii) a first binding curve, in which formation of a non-specific second ligand/solid phase complex is plotted versus time, does not level off;

(c) binding a detectable tag to said second ligand either prior to or after formation of said first ligand/analyte/second ligand complex so that a portion of said tag is retained on said solid phase upon formation of said first ligand/analyte/second ligand complex;

(d) detecting said retained tag to determine the presence or level of said analyte in said sample.

23. A method of detecting the presence or level of an analyte in a sample, the method comprising steps of:

(a) contacting said sample with:

(i) a solid phase having bound thereto a first ligand, which first ligand is characterized in that it binds to said analyte when incubated therewith, the contacting being performed so that a first ligand/analyte complex is formed on said solid phase; and

(ii) a second ligand that binds said first ligand/analyte/second ligand complex when incubated therewith, so that a first ligand/analyte/second ligand complex is formed on said solid phase, said contacting being performed under contacting being performed under conditions and for a time sufficiently limited that substantially no non-specific binding between said second ligand and said solid phase occurs;

(b) binding a detectable tag to said second ligand either prior to or after formation of said first ligand/analyte/second ligand complex so that a portion of said tag is retained on said solid phase upon formation of said first ligand/analyte/second ligand complex;

(c) detecting said retained tag to determine the presence or level of said analyte in said sample.

The references relied upon by the examiner are:

Woods et al. (Woods) 4,469,787 Sep. 4, 1984

Freytag et al. (Freytag), "Affinity-column-mediated immunoenzymometric assays: Influence of affinity-column ligand and valency of antibody-enzyme conjugates," Clin. Chem., Vol. 30, No. 9, pp. 1494-1498 (1984)

Friguet et al. (Friguet), "Measurements of the true affinity constant in solution of antigen-antibody complexes by enzyme-linked immunosorbent assay," Journal of Immunological Methods, Vol. 77, pp. 305-319 (1985)

Pollema et al. (Pollema), "Sequential injection immunoassay utilizing immunomagnetic beads," Anal. Chem., Vol. 64, pp. 1356-1361 (1992)

Grounds of Rejection

Claims 1-10 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

Claims 1-5, 8-14, 16-21 and 23-25 stand rejected under 35 U.S.C. § 103 as obvious over Pollema in view of Friguet and Woods.

Claims 6-7, 22 and 25 stand rejected as obvious over Pollema in view of Friguet and Woods, in further view of Freytag.

We reverse the rejection of claims 1-10 under 35 U.S.C. § 112, second paragraph and the rejections under 35 U.S.C. § 103.

DISCUSSION

In reaching our decision in this appeal, we have given careful consideration to the appellants' specification and claims, to the applied prior art references, and to the respective positions articulated by the appellants and the examiner.

Rather than reiterate the conflicting viewpoints advanced by the examiner and the appellants regarding the above-noted rejection, we make reference to the Examiner's Answer for the examiner's complete reasoning in support of the rejection, and to the appellants' Brief and Reply Brief for the appellants' arguments thereagainst. As a consequence of our review, we make the determinations which follow.

35 U.S.C. § 112, first paragraph

Claims 1-10 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite. It is the examiner's position that "a separation step is needed between steps (e) and (f) in order for detection to occurs [sic]. Further it is unclear how a portion of the tag retained on the solid phase can be detected and then compared to the same portion of the tag. Appellants' attention is directed to parts (e) and (f) in which the "portion of said tag" is recited." Answer, page 3.[1]

Whether a claim is indefinite depends upon whether those skilled in the art would understand what is claimed, or the scope or the bounds of the claim, when read in light of the specification. The threshold step in resolving this issue is to determine whether the examiner has met his burden of proof by advancing acceptable reasoning of indefiniteness. Appellants argue that one of ordinary skill in the art reading the

[1] The Answer includes duplicate page numbering. Page numbers referred to in the Answer herein are the actual sequential page numbers of the Answer.

specification would readily understand that no separation step is required. Reply Brief, page 2. In our view, with respect to the lack of a recited separation step in the claims, we find the examiner has not met his burden of proof by advancing acceptable reasoning of indefiniteness. For example, the examiner has made no reference to the specification indicating that such a separation step is required in the claimed method.

Moreover, we find that when the claim language, “portion of a tag,” is read in view of the disclosure, as required, its meaning is clear, and thus the metes and bounds of claim 1 are not indefinite. For example, the specification pages 20 states "Two signals are measured, one arising from the reference liquid and one arising from the sample.” Specification, pages 20-21. The phrase, “portion of a tag” would appear to refer to the tag retained on the solid phase upon formation of said first ligand/second ligand complex in the test sample. It is to be compared with the tag retained on the solid phase using a known amount of analyte to determine the presence or level of the analyte in the sample.

In view of the above, the rejection of claims 1-10 under 35 U.S.C. § 112, second paragraph as being indefinite is reversed.

35 U.S.C. § 103

Claims 1-5, 8-14, 16-21 and 23-25 stand rejected under 35 U.S.C. § 103 as obvious over Pollema in view of Friguet and Woods. Claims 6-7, 22 and 25 stand rejected over the above combination of references, in further view of Freytag.

It is the examiner's position that (Answer, pages 3-4):

> Pollema et al teach a sequential immunoassay for the investigation of a short-time kinetic study of antibody binding. Pollema et al teach using immunomagnetic beads as the solid phase surface which are coated with antibodies against the protein to be detected. ... The beads are packed into a reaction coil to form an immobilized reaction surface. Next, labeled protein is aspirated into the reaction coil, and the flow is stopped for a specified contact time. .... Following the stopped flow, unbound portion of the sample is measured to determine the amount of unbound labeled reagent present. this yield signal which can be related to the protein concentration. Pollema et al. tech a competitive binding reaction of a serum sample by "spiking" an unlabeled antibody with a known quantity of an identical FITC-labeled antibody. first the beads are placed into a magnetic field and held, next the spiked sample is introduced into the beads. ... This competitive assay is optimized if there is a slight excess of labeled antibodies for the sites available. Pollema also teach that in a sandwich assay, an excess of both labeled and unlabeled antibodies are used to drive the reaction to the maximum bound state. ...

The examiner finds that (Answer, page 5):

> Pollema et al differ from the instant invention in failing to specifically teach the steps of the competitive and sandwich immunoassays, and measuring the bound label as an indication of the amount of analyte present in the sample.

To remedy the deficiencies of Pollema, the examiner relies on Friguet. According to the examiner, Friguet teaches "an enzyme-linked immunosorbent assay involving mixing antigen (analyte) with an antigen-specific antibody (second ligand), contacting the resulting mixture with a solid phase coated with the antigen (first ligand), binding a detectable tag (a second antibody) to the antigen-specific antibody, and detecting the portion of the tag bound to the solid phase (bound to the first ligand/second ligand complexes to the solid phase)". Answer, page 5. Friguet

teaches "mixing similar concentrations of analyte and antibody, and performing the contacting step under conditions and for a time sufficiently limited that no readjustment of the liquid phase equilibrium occurs during the step of contacting the mixture with the solid phase".... Id.

Woods is relied on by the examiner for the disclosure of "a method for quantitatively determining the presence of a ligand in a sample in a sandwich immunoassay" ... Id.

The examiner summarizes (Answer, pages 5-6)

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the assay of Friguet et al using the sequential injection method and short contact time taught by Pollema et al because Pollema et al teach that sequential injection offers several advantages for immunoassays. The highly reproducible timing obtained with the sequential injection allows for accurate analysis that can extend into non-equilibrium measurements in a very short time frame not generally considered or achieved by a batch technique. Sequential injection accelerates sample handling, which in batch method is too slow thus preventing the utilization of short-time kinetics. Stop-flow techniques enhance the usefulness of immunoassay by allowing well-controlled contact times between antibody and antigen, which can range from only a fraction of a second into the traditional equilibrium time frame.

The examiner also finds the fact that the contacting step in Pollema is inherently "performed for a time so that equilibrium is not reached and the binding curve does not level off".... Answer, page 6.

We do not find the examiner has presented sufficient evidence to support a prima facie case of obviousness.

Pollema teaches a sequential injection immunoassay (SIA) which utilizes

immunomagnetic beads to investigate short-time antibody binding. The SIA assay format is entirely different from that of the claimed invention, as acknowledged by the examiner on page 5 of the Answer. At first blush, the Pollema reference looks relevant because of its emphasis on short-time binding kinetics, i.e., measuring analyte/antibody binding in that limited window of time before non-selective binding and/or dissociation-reassociation become a factor. According to Pollema, the stop flow techniques described therein enhance the usefulness of the sequential injection immunoassay by allowing well-controlled contact times between antibody and antigen, which can range from only a fraction of a second into the traditional equilibrium time frame. Pollema, page 1391. In addition, Pollema suggests rather generically that the "technique is quite flexible and should be adaptable to most of the detection schemes which have been utilized for clinical immunoassays. Pollema, page 1356, column 2. However, reading the reference in its entirety, it is clear that the "technique" to which Pollema refers here is that of the steps of the "sequential injection immunoassay" and not any specific time frame of the SIA technique. Interestingly, the entire SIA assay time of Pollema would appear to be about 120 seconds. Pollema, page 1358, column 2.

Friguet is cited by the examiner for the disclosure of a competitive ELISA assay which allows the determination of the dissociation constant of the antigen-monoclonal antibody equilibrium in solution, provided it is used after the equilibrium is reached to measure the amount of free antibody in solution. Friguet, page 306. Thus, the Friguet assay must be conducted after equilibrium is reached. In contrast, the claimed

method of detecting the presence or level of an analyte in a sample is conducted "for a time sufficiently limited that substantially no dissociation of said analyte/second ligand complexes occurs while said mixture is in contact with said solid phase", i.e. equilibrium is not reached.

Appellants argue there is "no teaching, suggestion or motivation from Pollema, Friguet and Woods references, alone or in combination, with the knowledge of ordinary skill in the art, to arrive at the claimed subject matter." Brief, sequential page 11. We agree with appellants that the examiner has not provided evidence of sufficient motivation to combine Pollema and Friguet.

First, the examiner admits that the SIA format of Pollema is not the claimed assay format. Second, the assay of Friguet must be conducted after the antigen and monoclonal antibody reach equilibrium in solution. Third, the alleged section of Pollema on which the examiner relies to support or provide motivation for using the "technique" of Pollema in other assay formats such as that of Friguet, in our view, has been misconstrued by the examiner to refer to "short-time antibody binding" when the "technique" referred to is that of the sequential injection immunoassay. We do not find that the examiner has provided an indication of an appropriate reason, suggestion or motivation, in either Friguet or Pollema, to conduct the competitive ELISA assay of Friguet at a time other than after equilibrium has been reached between the antigen

and antibody. In our view, the only suggestion to combine the cited references comes from appellants' disclosure.

The Federal Circuit has stated that "[the] mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." In re Fritch, 972 F.2d 1260, 1266 n.14, 23 USPQ2d 1780, 1783-84 n.14 (Fed. Cir. 1992), citing In re Gordon, 773 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984). The Federal Circuit also has found that if a rote invocation of a high level of skill in the art could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. "To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness." In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). Moreover, the use of hindsight in the selection of references that comprise the case of obviousness is forbidden. In re Gorman, 933 F.2d 982, 986, 18 USPQ2d 1885, 1888 (Fed. Cir. 1991).

In the present case, the examiner has failed to indicate the specific understanding or principle within the knowledge of a skilled artisan, explicit or implicit, that would have motivated one with no knowledge of appellant's invention to make the combination in the manner claimed. In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313,

1316 (Fed. Cir. 2000). Thus, with respect to claims 1 and 20 which define a competitive assay format, we do not find the combination of Pollema and Friguet to support a prima facie case of obviousness.

With respect to claims 11 and 23, our review of the examiner's rejections and analysis in the present case have been made difficult, as the examiner has failed to provide analysis as to why each of the claims argued separately by appellants is rejected. The examiner has failed to separately argue the rejection of each claim in the Answer. As best we can determine Woods is relied on by the examiner solely for the purpose of rejection of the sandwich assay claims 11 and 23.

As with the assay of Friguet, the sandwich assay of Woods would reasonably appear to be conducted when equilibrium between the antigen and antibody is reached. For example, the assay time of Example 1 of Woods requires an incubation time of one hour. Woods, column 7, line 15.

We do not find that the examiner has provided an indication of an appropriate reason, suggestion or motivation, in either Woods or Pollema, to conduct the sandwich assay of Woods at a time other than after equilibrium has been reached between the antigen and antibody. In our view, the only suggestion to combine the cited references comes from appellants' disclosure. We agree with appellants that the examiner has not provided evidence of sufficient motivation to combine Pollema and Woods. Nor do we find that Freytag, describing an affinity-column-mediated immunoenzyomemetric assay with a dwell time of 75-120 seconds (page 1497, column 2) to overcome the

deficiencies of the primary combination of references. The rejections of the claims for obviousness are reversed.

CONCLUSION

The rejection of claims 1-10 under 35 U.S.C. § 112, second paragraph as being indefinite, is reversed.

The rejection of claims 1-5, 8-14, 16-21 and 23-25 under 35 U.S.C. § 103 as obvious over Pollema in view of Friguet and Woods; and the rejection of claims 6-7, 22 and 25 as obvious over Pollema in view of Friguet and Woods, in further view of Freytag are reversed.

REVERSED

WILLIAM F. SMITH	)
Administrative Patent Judge	)
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TONI R. SCHEINER	)
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	)
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